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Interval from the Onset of Transmitral Flow to Annular Velocity Is a Marker of LV Filling Pressure

Recently, the time interval between the onset of early diastolic transmitral flow velocity (E) and mitral annular velocity (e′) ($T_{E-e'}$) was proposed as a new index representing left ventricular (LV) relaxation. A problem with the measurement of $T_{E-e'}$ was that E and e′ could not be measured in the same beat. However, a novel dual Doppler echocardiographic method has been introduced that allows the measurement of both E and e′ in the same beat (1), and E/e′ and $T_{E-e'}$ can be instantly calculated. The aims of this study were to: 1) investigate the usefulness of single-beat $T_{E-e'}$ compared with invasive hemodynamic measurements; and 2) determine the impact of pre-load alterations by leg-positive pressure (LPP) on the relationship between $T_{E-e'}$ and increased LV filling pressure.

We designed a prospective study to assess 42 consecutive patients who underwent catheterization for diagnosis of stable angina pectoris. Twenty-one age- and sex-matched healthy volunteers served as the control group. Patients with atrial fibrillation, valve diseases, severe heart failure, LV systolic dysfunction (LV ejection fraction <40%), or a regional wall motion abnormality at the basal, lateral, or septal region were excluded.

A total of 63 pairs of echocardiographic examinations were performed at baseline and during LPP. We used an ultrasound machine EUB-7500 (Hitachi Medical Corporation, Kashiwa, Japan). A 5-F Millar transducer with single lumen was introduced into the LV. Tau and LV end-diastolic pressure (LVEDP) were determined from the LV pressure curve, and measurements were performed simultaneously with the echocardiographic measurements. We customized a commercially available leg massage machine (Dr. Medomer DM-5000EX, Medo Industries, Tokyo, Japan) because it could maintain the same pressure loading (90 mm Hg) for 5 min.

Values are expressed as mean ± SD. The diagnostic ability of echocardiographic parameters to discriminate elevated LVEDP (>16 mm Hg) was determined by analysis of receiver-operating characteristic (ROC) curves. Reproducibility was expressed as the intraclass correlation coefficients (ICC) in a group of 10 randomly selected subjects by 1 observer, and then repeated on 2 separate days by 2 investigators.

The clinical characteristics and the influence of LPP in both groups are shown in Table 1. A representative case is shown in Figure 1. There was a correlation between $T_{E-e'}$ and LVEDP at baseline ($r = 0.71$, $p < 0.001$) and during LPP ($r = 0.82$, $p < 0.001$). There was also a relationship between the change in LVEDP in response to LPP and the change in $T_{E-e'}$ ($r = 0.50$, $p < 0.001$). The $T_{E-e'}$ (standardized beta = 0.73, $p < 0.001$ at baseline and standardized beta = 0.89, $p < 0.001$ during LPP) was an independent predictor of the LVEDP in multivariate regression analysis with adjustment for age and sex. A ROC curve (area under the curve [AUC] = 0.93) was used to select a $T_{E-e'}$ cutoff of 38 ms (specificity: 91%; sensitivity: 85%) to predict elevated LVEDP (>16 mm Hg) during LPP. For differentiating elevated LVEDP during LPP, the AUC was significantly higher for the $T_{E-e'}$ compared with E/e′ (AUC = 0.93 vs. AUC = 0.72, $p = 0.004$). The $T_{E-e'}$ (standardized beta = 0.42, $p = 0.011$ at baseline and standardized beta = 0.71, $p < 0.001$ during LPP) were also independent predictors of tau in multivariate regression analysis with adjustment for age and sex. The ICC of intraobserver variability was 0.98 ($p < 0.001$), and interobserver variability was 0.95 ($p < 0.001$).

This study is the first to demonstrate that single-beat $T_{E-e'}$ correlated with invasively measured LV diastolic pressure, and that the $T_{E-e'}$ was a better predictor of LV filling pressure than E/e′. In addition, our study showed that $T_{E-e'}$ is pre-load–dependent compared with other Doppler parameters of LV diastolic function. $T_{E-e'}$ could be influenced by pre-load changes, especially with impaired LV relaxation.

We postulate that because the mitral E begins with the crossing of left atrial (LA) and LV pressures, an augmentation of LA pressure might shorten the time needed for LA and LV pressures to cross, and this would shorten the isovolumic relaxation time. The onset of e′ is influenced by LV active relaxation and the cardiac restoring forces in end diastole. As LV relaxation is delayed and early diastolic suction is reduced, the onset of e′ is delayed and follows the onset of the E wave. In addition, an augmentation in pre-load might prolong the duration of systole and delay the onset of e′. For these reasons, $T_{E-e'}$ was prolonged by a pre-load increase. The main limitation of this study was the small number of patients with elevated LVEDP at baseline (8 of 42).

Elevation of LVEDP prolongs $T_{E-e'}$, and this may be due to enhanced early diastolic mismatch between mitral inflow and annular motion. $T_{E-e'}$ is a sensitive noninvasive index for the estimation of LVEDP, and dual Doppler echocardiography is a practical method for the accurate measurement of this index in a single beat.

Kenya Kusunose, MD, PhD, Hirotsugu Yamada, MD, PhD,* Susumu Nishio, RMS, Rina Tamai, RMS, Toshiyuki Niki, MD, Koji Yamaguchi, MD, PhD, Yoshio Taketani, MD, Takashi Iwase, MD, PhD, Takeshi Soeki, MD, PhD, Tetsuzo Wakatsuki, MD, PhD, Masataka Sata, MD, PhD

*Department of Cardiovascular Medicine, Tokushima University Hospital, 2-50-1 Kuramoto, Tokushima, Japan.
E-mail: *yamadah@tokushima-u.ac.jp*.

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Table 1. Influence of Lower Positive Pressure (LPP) on Echocardiographic Parameters

	Control Group (n = 21)			Patient Group (n = 42)		
	Baseline	LPP	p Value	Baseline	LPP	p Value
Age, yrs	68 ± 6			69 ± 5		
Male	15 (71)			29 (69)		
Hemodynamic data						
Systolic BP, mm Hg	122 ± 18	124 ± 21	NS	135 ± 20*	134 ± 22	NS
Diastolic BP, mm Hg	66 ± 12	69 ± 14	NS	73 ± 11*	72 ± 7	NS
Heart rate, beats/min	62 ± 8	62 ± 10	NS	69 ± 6*	70 ± 5	NS
LA and LV dimensions and function						
LVEDV, ml	75 ± 14	78 ± 16	<0.05	92 ± 27*	96 ± 30	<0.05
LVESV, ml	26 ± 8	27 ± 9	NS	38 ± 17*	40 ± 19	NS
LA volume index, ml/m^2	16 ± 9	21 ± 10	<0.01	36 ± 11*	41 ± 10	<0.001
Ejection fraction, %	66 ± 11	67 ± 11	NS	58 ± 14*	60 ± 15	NS
LV mass index, g/m^2	117 ± 13			135 ± 24*		
IVC, cm	0.9 ± 0.5			1.0 ± 0.4		
E wave, cm/s	62 ± 10	71 ± 11	<0.001	84 ± 11	97 ± 12	<0.001
A wave, cm/s	66 ± 14	77 ± 18	<0.05	89 ± 17	91 ± 20	NS
E-DT, ms	236 ± 34	228 ± 41	NS	242 ± 69	230 ± 66	<0.001
E/A	0.92 ± 0.13	0.96 ± 0.14	NS	0.99 ± 0.35	1.13 ± 0.37	<0.001
E′, cm/sec	9.1 ± 3.0	10.8 ± 2.6	<0.05	7.7 ± 2.6*	8.1 ± 2.5	NS
E/e′	7.4 ± 0.5	7.6 ± 0.8	NS	11.9 ± 3.5*	13.1 ± 3.7	<0.05
$T_{E\text{-}e}$′, ms	5 ± 8	12 ± 7	<0.01	18 ± 18*	42 ± 16	<0.001
Invasive hemodynamic data						
LVEDP, mm Hg				13.0 ± 3.2	16.2 ± 3.0	<0.001
Tau, ms				42.3 ± 8.7	43.8 ± 8.3	NS

Values are mean ± SD or n (%). *p <0.05, control group versus patient group. Differences between the 2 groups were assessed by a 2-tailed Student *t* test and chi-square test. Paired Student *t* test was used to assess the echocardiographic and other parameters at baseline and during LPP.
BP = blood pressure; DT = deceleration time of E wave; e′ = early diastolic mitral annular velocity; E = early diastolic transmitral flow velocity; IVC = inferior vena cava; LA = left atrium; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; Tau = time constant of the LV pressure decay during isovolumic diastole; $T_{E\text{-}e'}$ = the time interval between the onsets of E and e′.

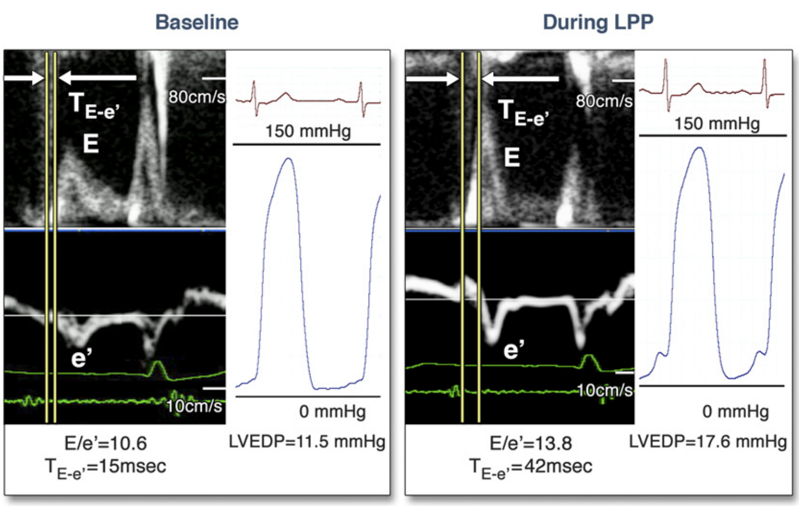

Figure 1. Representative Case of a 68-Year-Old Man

A 68-year-old male underwent catheterization. Measurement of the time interval between the onset of early diastolic transmitral flow velocity (E) and mitral annular velocity (e′) ($T_{E\text{-}e'}$) is shown. The E velocity, E/e′, $T_{E\text{-}e'}$ and left ventricular end-diastolic pressure (LVEDP) increased and the A velocity decreased during leg positive pressure (LPP).

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Defining Normative Values for 3D LV Volumes

The Devil Is in the Details

In their population-based study, Chahal et al. (1) reported average values of 49 ± 9 ml/m^2 and 42 ± 8 ml/m^2 for 3-dimensional echocardiography (3DE) end-diastolic volumes (EDV) in healthy European men and women, respectively. These volumes are significantly lower than those reported by other researchers who performed similar studies: 66 ± 10 ml/m^2 and 58 ± 8 ml/m^2, respectively, found by Aune et al. (2); and 55 ± 7 ml/m^2 and 49 ± 6 ml/m^2, respectively, reported by Kaku et al. (3) for the same age group. Even Fukuda et al. (4), who studied a Japanese population (significantly smaller body size than Europeans), found larger EDV: 50 ± 12 ml/m^2 and 46 ± 9 ml/m^2 in men and women, respectively. Interestingly, none of these previous studies has been referenced and discussed by Chahal et al. (1).

On the other end, the upper normal values (mean values ±2 SD) for 3D end-diastolic and end-systolic volumes reported by Chahal et al. (1) (e.g., 67 ml/m^2 and 29 ml/m^2, respectively, in males) are lower than the 2-dimensional echocardiography (2DE) upper normal limits reported in current guidelines (75 ml/m^2 and 30 ml/m^2, respectively) (5), contradicting all previous studies showing a greater underestimation of volumes measured by 2DE than by 3DE. Finally, making a simple calculation from the data provided in Table 1 in that paper (1), it seems that the European subjects were in low-flow state (stroke volume index 30 ml/m^2 in men and 26 ml/m^2 in women).

These data raise the issue of the accuracy of the measurements performed in this study, particularly when no reference (or at least comparison) modality, such as the simple stroke volume measured with 2DE and Doppler, has been provided. One possible explanation of the underestimation of the left ventricular volumes reported by Chahal et al. (1) may be the limited experience of the sonographers who performed measurements as stated by the authors (“ . . . all underwent a 4-week period of training in 3DE volume acquisition and off-line analysis by the vendor representative at the beginning of the study”) and underlined in the accompanying editorial (6). The effect of the reader experience on accuracy of 3D left ventricular volume measurements has been documented (7).

We concur with the idea that development of normative values is the first step for effective application of 3DE in clinical routine (6), and a meta-analysis of existing data could be a good start (8). However, there is a clear need to check the reliability of the data, too. Comparison with existing data and internal validation with stroke volume obtained by 2D and Doppler echocardiography may be a simple and practical way of checking results.

“However beautiful the strategy,
you should occasionally look at the results.”

—Sir Winston Churchill (9)

Luigi P. Badano, MD

Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Via Giustiniani 2, Padua, Padua 35123, Italy. *E-mail:* lpbadano@gmail.com

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REPLY

We thank Dr. Badano for showing an interest in our study and also for highlighting 2 other studies which we believe, despite being obviously dissimilar in design, report similar mean 3-dimensional echocardiographic (3DE) indexed left ventricular (LV) volumes as we observed in our European white subjects.

The study by Kaku et al. (1) recruited 322 hospital employees, relatives of employees, or volunteers from 3 institutions in America and Japan; among subjects 40 to 59 years of age, they reported end-diastolic volume index (EDVi) values of 55 ± 7 ml/m^2 and 49 ± 6 ml/m^2, respectively, for men and women, with an inferred stroke volume index (SVI) of ~35 ml/m^2. In the JAMP-3D (Japanese Normal Values for Echocardiographic Measurements Project) study (2), Fukuda et al. recruited 410 volunteers from 23 institutions (~18 studies per institution), using 6 different ultrasound platforms that required 4 different software packages for volume analysis. They reported EDVi values of 50 ± 12 ml/m^2 and 46 ± ml/m^2, with SVIs of 34 and 36 ml/m^2, respectively, for men